

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 October 2005 (27.10.2005)

PCT

(10) International Publication Number
WO 2005/099353 A3

(51) International Patent Classification:
C07D 413/10 (2006.01) C07D 263/20 (2006.01)

MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(21) International Application Number:
PCT/IN2004/000105

(22) International Filing Date: 19 April 2004 (19.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): SYMED
LABS LIMITED [IN/IN]; 8-3-166 / 6 & 7, II Floor,
Sree Arcade, Erragadda, Hyderabad, Andhrapradesh,
Hyderabad 500 018 (IN).

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM; ZW),
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(72) Inventors; and
(75) Inventors/Applicants (for US only): MOHAN RAO,
Dodda [IN/IN]; 8-3-166 / 6 & 7, II Floor, Sree Arcade,
Erragadda, Hyderabad, Andhrapradesh, Hyderabad 500
018 (IN). KRISHNA REDDY, Pingli [IN/IN]; 8-3-166
/ 6 & 7, II Floor, Sree Arcade, Erragadda, Hyderabad,
Andhrapradesh, Hyderabad 500 018 (IN).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KB,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,

(88) Date of publication of the international search report:
26 October 2006

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette

(54) Title: A NOVEL PROCESS FOR THE PREPARATION OF LINEZOLID AND RELATED COMPOUNDS

(57) Abstract: The present invention provides a novel process for preparation of 5-aminomethyl substituted oxazolidinones, key intermediates for oxazolidinone antibacterials including linezolid. Thus linezolid is prepared by a) reacting 3-fluoro-4-morpholinyl aniline with R-epichlorohydrin; b) subjecting N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline produced above to carbonylation; c) reacting (5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone produced above with potassium phthalimide; d) reacting (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]phthalimide produced above with hydrazine hydrate; and e) reacting S-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine produced above with acetic anhydride to produce linezolid.

WO 2005/099353 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2004/000105

A. CLASSIFICATION OF SUBJECT MATTER IPC ⁸ : C07D 413/10 (2006.01); C07D 263/20 (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC ⁸ : C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched _____ Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPI, EPODOC, PAJ, REGISTRY, CAPLUS, CASREACT		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US5688792 A (BARBACHYN M R et al.) 18 November 1997 (18.11.1997); cited by the applicant. <i>abstrac</i>	1-58
A	US5837870 A (BABACHEN M R et al.) 17 November 1998 (17.11.1998); cited by the applicant. <i>abstract</i>	1-58
A	WO1999/24393 A1 (PHARMACIA & UPJOHN CO) 20 May 1999 (20.05.1999); cited by the applicant. <i>abstract, claims</i>	1-58
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 1 August 2006 (01.08.2006)		Date of mailing of the international search report 25 August 2006 (25.08.2006)
Name and mailing address of the ISA/ AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No +43 / 1 / 534 24 / 535		Authorized officer MÜLLER-HIEL R. Telephone No +43 / 1 / 534 24 / 434

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2004/000105

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO1995/07271 A1 (PHARMACIA & UPJOHN CO) 16 March 1995 (16.03.1995); cited by the applicant <i>abstract, claim 1</i>	1-58
A	Brickner, Steven J. et al. " Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections " Journal of Medicinal Chemistry (1996), 39(3), 673-9 (abstract). CAPLUS [online] Copyright 2006 ACS on STN [retrieved on 1 August 2006 (01.08.2006)]. Retrieved from: STN International, Karlsruhe. Accession No. 1996:58412 CAPLUS; cited by the applicant <i>abstract</i>	1-58
A	Lohray, Braj B. et al. " A short synthesis of oxazolidinone derivatives Linezolid and Eperezolid: a new class of antibacterials " Tetrahedron Letters (1999), 40(26), 4855-4856 (abstract). CAPLUS [online] Copyright 2006 ACS on STN [retrieved on 1 August 2006 (01.08.2006)]. Retrieved from: STN International, Karlsruhe. Accession No. 1999:429192 CAPLUS; cited by the applicant. <i>abstract</i>	1-58
A	Krishna Reddy, K. V. S. R. et al. "Isolation and characterization of process-related impurities in linezolid " Journal of Pharmaceutical and Biomedical Analysis (2002), 30(3), 635-642 (abstract). CAPLUS [online] Copyright 2006 ACS on STN [retrieved on 1 August 2006 (01.08.2006)]. Retrieved from: STN International, Karlsruhe. Accession No. 2002:742207 CAPLUS. <i>abstract</i>	1-58
A	JP9278722 A (POLA CHEM IND INC) 28 October 1997 (28.10.1997) <i>abstract</i>	1-58
A	EP1050532 A2 (AEROJET FINE CHEM LLC) 8 November 2000 (08.11.2000) <i>abstract, paragraphs [0047], [0073]</i>	1-58

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN 2004/000105

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
A			none		
EP	A2 1050532	2000-11-08	US	A1 2005171170	2005-08-04
			US	A1 2003225292	2003-12-04
			DE	T2 60013021T	2005-09-01
			DE	D1 60013021D	2004-09-23
			US	B1 6605732	2003-08-12
JP A 9278722A2			none		
US	A 5688792	1997-11-18	NL	I1 300079I	2002-04-02
			DE	I1 10299007I	2002-07-04
			GR	T3 3031809T	2000-02-29
			US	A 5880118	1999-03-09
			SI	T1 717738T	2000-02-29
US	A 5837870		US	A1 2002095054	2002-07-18
			NO	A 20015253	1998-12-09
			HK	A1 1018785	2002-11-22
			KR	A 2000005358	2000-01-25
			NO	A 984737	1998-12-09
			ZA	A 9702983	1998-10-08
WO	A 9507271		NL	I1 300079I	2002-04-02
			DE	I1 10299007I	2002-07-04
			LV	A 12605	2001-01-20
			GR	T3 3031809T	2000-02-29
			US	A 5880118	1999-03-09
			IL	A 110802	2000-09-28
WO	A 9924393		US	A1 2004006238	2004-01-08
			US	A1 2003216572	2003-11-20
			US	A1 2003130509	2003-07-10
			US	A1 2003065219	2003-04-03
			US	A1 2002095054	2002-07-18
			US	A1 2002032348	2002-03-14